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(21) International Application Number: PCT/US98/19359 (22) International Filing Date: 16 September 1998 (16.09.98) (30) Priority Data: 60/061,383 7 October 1997 (07.10.97) US (71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): DEERING, Carl, Francis [US/US]; 2688 Kragspough Court, Holland, MI 49424 (US). MENNEN, Kenneth, Earl [US/US]; 66 W. 26th Street, Holland, MI 49423 (US). RAMAGE, Robert [GB/GB]; 26 Craigleith View, Edinburgh EH4 3JZ (GB). (74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: PROCESS FOR PREPARING A CYCLIC AMINO ACID ANTICONVULSANT COMPOUND (57) Abstract An improved process for the preparation of a cyclic amino acid by a novel synthesis is described where benzonitrile is treated with an alkali metal and an amine under Birch reduction conditions to generate in situ an anionic intermediate which is alkylated with an α -haloacetic acid moiety which is subsequently converted to the desired product, as well as valuable intermediates used in the process.		

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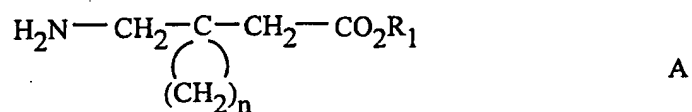
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PROCESS FOR PREPARING A CYCLIC AMINO ACID
ANTICONVULSANT COMPOUND

BACKGROUND OF THE INVENTION

United States Patent Numbers 4,024,175 and 4,087,544, which are herein
5 incorporated by reference, disclose novel cyclic amino acids of Formula A



wherein R₁ is a hydrogen atom or a lower alkyl radical, and n is 4, 5, or 6 and the pharmacologically compatible salts thereof.

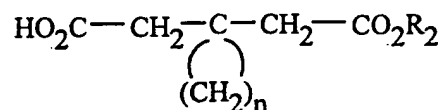
The compounds disclosed in the above United States patents are useful for
10 the therapy of certain cerebral diseases, for example, they can be used for the treatment of certain forms of epilepsy, faintness attacks, hypokinesia, and cranial traumas. Additionally, they bring about an improvement of cerebral functions, and thus are useful in treating geriatric patients. Particularly valuable is
1-(aminomethyl)-cyclohexaneacetic acid (gabapentin).

15 Gamma-aminobutyric acid (GABA) is an inhibitory amino acid found in the mammalian central nervous system (CNS). It has been reported that dysfunction with GABA neurotransmission in the CNS may contribute or even cause psychiatric and neurological diseases such as epilepsy, schizophrenia, Parkinson's disease, Huntington's Chorea, and dyskinesia (Saletu B., et al.,
20 International Journal of Clinical Pharmacology, Therapy and Toxicology, 1986;24:362-373). Gabapentin was designed as a GABA analog that would cross the blood-brain barrier. Gabapentin was found to have anticonvulsant and antispastic activity with extremely low toxicity in man.

United States Patent Number 5,084,479 discloses the use of gabapentin in
25 neurodegenerative disorders. United States Patent Number 5,025,035 discloses the use of gabapentin in depression. United States Patent Number 5,510,381 discloses the use of gabapentin in mania and bipolar disorders.

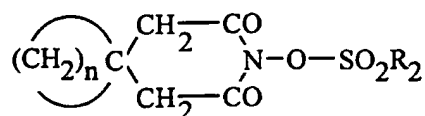
-2-

The aforementioned compounds of Formula A including gabapentin have been prepared from a compound of formula



wherein R_2 is an alkyl radical containing up to eight carbon atoms, and n is as defined above by well-known standard reactions such as, for example, the Hofmann, Curtius, or Lossen rearrangements into the amino derivatives of Formula A. Although these reactions provide the target compounds, they require a large number of synthetic steps and in some cases involve potentially explosive intermediates.

United States Patent Number 4,152,326 discloses cyclic sulphonyloxyimides of formula



wherein R_2 is a saturated, straight-chained, branched or cyclic lower aliphatic radical or an unsubstituted or substituted aryl radical, and n is 4, 5, or 6, which can be converted into a compound of Formula A. Again, similar to the previous processes, this process requires a large number of synthetic steps to obtain a compound of Formula A. Finally, all of the previous processes require as the penultimate step conversion of an intermediate salt of the target compound to an amino acid of Formula A.

United States Patent Numbers 5,132,451, 5,319,135, 5,362,883, 5,091,567, 5,068,413, 4,956,473, 4,958,044, 5,130,455, 5,095,148, 5,136,091, and 5,149,870 disclose additional processes and intermediates for preparing gabapentin. These processes require a number of steps and in some cases utilize large quantities of hazardous materials.

-3-

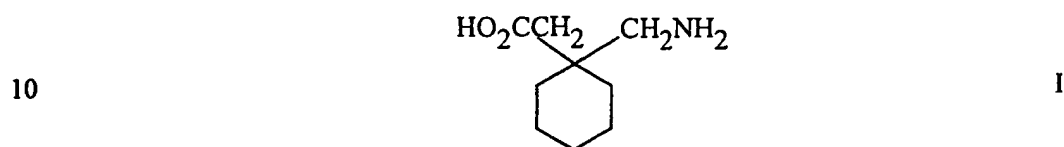
The object of the present invention is an improved process for preparing gabapentin employing a novel synthesis.

Further, we have unexpectedly found that gabapentin can be prepared from novel intermediates in fewer steps and higher yields than the previous methods.

5 Moreover, the present method proceeds from inexpensive starting materials and is amenable to large-scale synthesis.

SUMMARY OF THE INVENTION

Accordingly, a first aspect of the present invention is an improved process for the preparation of the compound of Formula I

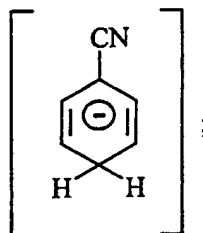


which comprises:

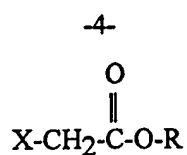
Step (a) treating the compound of Formula VII



15 with an alkali metal in ammonia or higher order amine in the presence of a solvent to afford in situ the compound of Formula VI

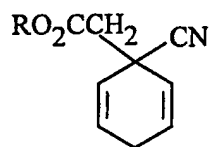


Step (b) treating the compound of Formula VI with a compound of Formula V



V

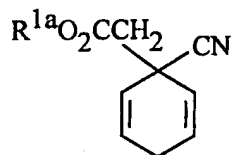
- 5 wherein X is halo or sulfonate and R is hydrogen, an alkali metal, an alkaline earth metal, ammonium, an amine cation, alkyl, or benzyl in the presence of a solvent to afford a compound of Formula IV



IV

wherein R is as defined above;

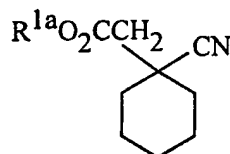
Step (c) treating a compound of Formula IVa



IVa

10

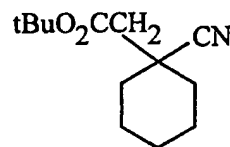
wherein R^{1a} is alkyl with hydrogen in the presence of a catalyst and a solvent to afford a compound of Formula III



III

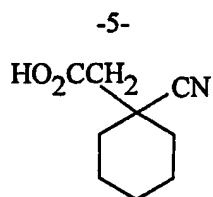
wherein R^{1a} is as defined above;

- 15 Step (d) treating the compound of Formula IIIa



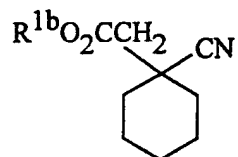
IIIa

with an acid in a solvent to afford the compound of Formula II



II

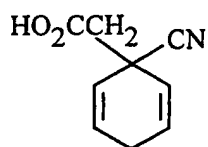
or treating a compound of Formula IIIb



IIIb

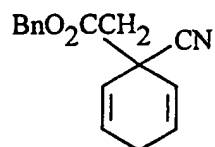
wherein R^{1b} is alkyl excluding tertiary butyl with an acid or base in a solvent to afford the compound of Formula II or treating the compound of Formula IVb

5



IVb

with hydrogen in the presence of a catalyst and a solvent to afford the compound of Formula II or treating the compound of Formula IVc

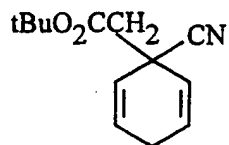


IVc

with hydrogen in the presence of a catalyst and a solvent to afford the compound of Formula II;

10

Step (e) treating the compound of Formula IVa-1

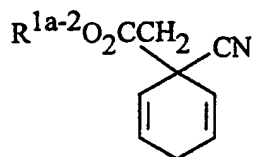


IVa-1

with an acid in a solvent to afford the compound of Formula IVb or treating a compound of Formula IVa-2

15

-6-



IVa-2

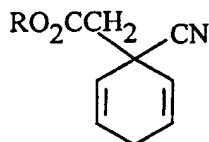
wherein R^{1a-2} is alkyl excluding tertiary butyl with an acid or base in a solvent to afford the compound of Formula IVb; and

Step (f) treating either the compound of Formula IVb

5 or the compound of Formula IVc

or the compound of Formula II with hydrogen in the presence of a catalyst and a solvent to afford the compound of Formula I.

A second aspect of the present invention is an improved process for the preparation of a compound of Formula IV

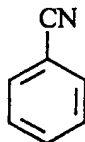


IV

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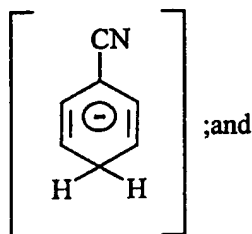
wherein R is hydrogen, an alkali metal, an alkaline earth metal, ammonium, an amine cation, alkyl, or benzyl which comprises:

Step (a) treating the compound of Formula VII



VII

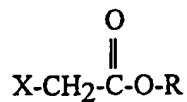
15 with an alkali metal in ammonia or higher order amine in the presence of a solvent to afford in situ the compound of Formula VI



VI

-7-

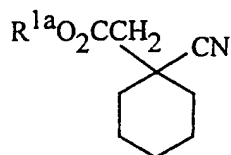
Step (b) treating the compound of Formula VI with a compound of Formula V



V

- 5 wherein X is halo or sulfonate and R is hydrogen, an alkali metal, an alkaline earth metal, ammonium, an amine cation, alkyl, or benzyl in the presence of a solvent to afford a compound of Formula IV.

A third aspect of the present invention is an improved process for the preparation of a compound of Formula III

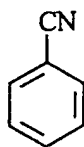


III

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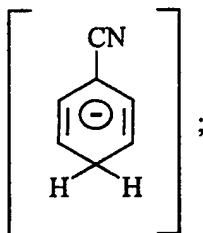
wherein R^{1a} is alkyl which comprises:

Step (a) treating the compound of Formula VII



VII

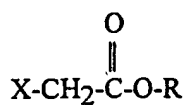
- 15 with an alkali metal in ammonia or higher order amine in the presence of a solvent to afford in situ the compound of Formula VI



VI

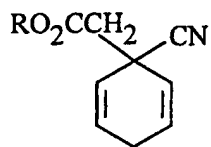
Step (b) treating the compound of Formula VI with a compound of Formula V

-8-



V

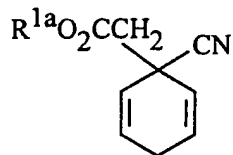
- 5 wherein X is halo or sulfonate and R is hydrogen, an alkali metal, an alkaline earth metal, ammonium, an amine cation, alkyl, or benzyl in the presence of a solvent to afford a compound of Formula IV



IV

wherein R is as defined above; and

Step (c) treating a compound of Formula IVa

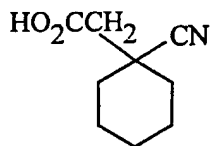


IVa

10

wherein R^{1a} is alkyl with hydrogen in the presence of a catalyst and a solvent to afford a compound of Formula III.

A fourth aspect of the present invention is an improved process for the preparation of the compound of Formula II

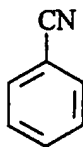


II

15

which comprises:

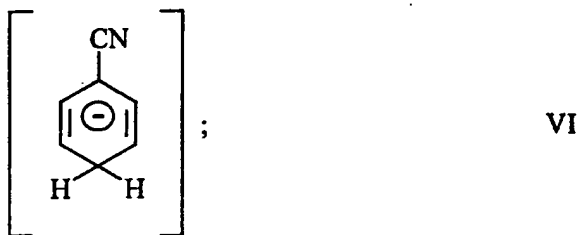
Step (a) treating the compound of Formula VII



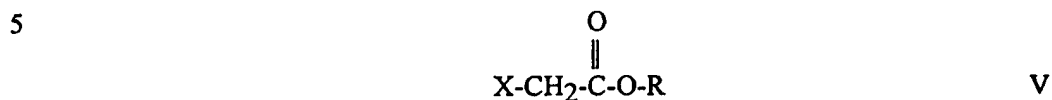
VII

-9-

with an alkali metal in ammonia or higher order amine in the presence of a solvent to afford in situ the compound of Formula VI



Step (b) treating the compound of Formula VI with a compound of Formula V



wherein X is halo or sulfonate and R is hydrogen, an alkali metal, an alkaline earth metal, ammonium, an amine cation, alkyl, or benzyl in the presence of a solvent to afford a compound of Formula IV



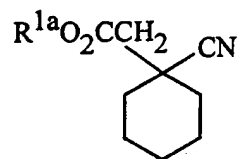
wherein R is as defined above;

Step (c) treating a compound of Formula IVa



wherein R^{1a} is alkyl with hydrogen in the presence of a catalyst and a solvent to afford a compound of Formula III

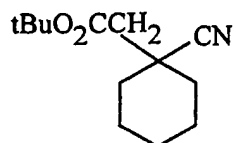
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III

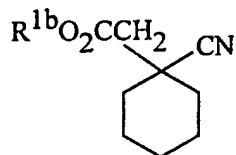
wherein R^{1a} is as defined above; and

Step (d) treating the compound of Formula IIIa



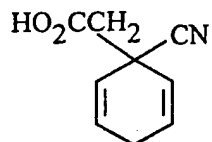
IIIa

- 5 with an acid in a solvent to afford the compound of Formula II or treating a compound of Formula IIIb



IIIb

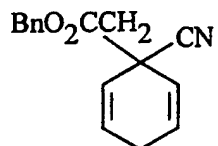
wherein R^{1b} is alkyl excluding tertiary butyl with an acid or base in a solvent to afford the compound of Formula II or treating the compound of Formula IVb



IVb

10

with hydrogen in the presence of a catalyst and a solvent to afford the compound of Formula II or treating the compound of Formula IVc

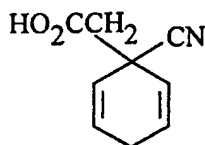


IVc

-11-

with hydrogen in the presence of a catalyst and a solvent to afford the compound of Formula II.

A fifth aspect of the present invention is an improved process for the preparation of the compound of Formula IVb

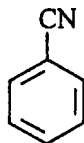


5

IVb

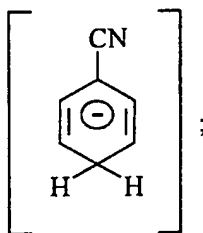
which comprises:

Step (a) treating the compound of Formula VII

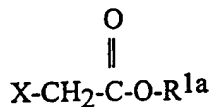


VII

10 with an alkali metal in ammonia or higher order amine in the presence of a solvent to afford in situ the compound of Formula VI



Step (b) treating the compound of Formula VI with a compound of Formula Va

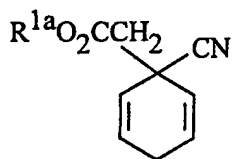


15

Va

wherein X is halo or sulfonate and R^{1a} is alkyl, in the presence of a solvent to afford a compound of Formula IVa

-12-



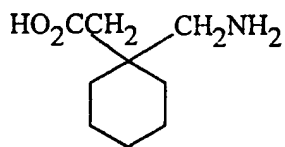
IVa

wherein R^{1a} is as defined above; and

Step (c) treating a compound of Formula IVa

with an acid or base in a solvent to afford the compound of Formula IVb

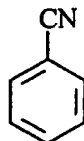
- 5 A sixth aspect of the present invention is an improved process for the preparation of the compound of Formula I



I

which comprises:

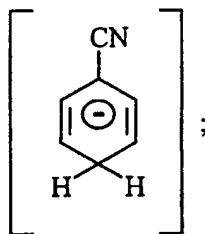
Step (a) treating the compound of Formula VII



VII

10

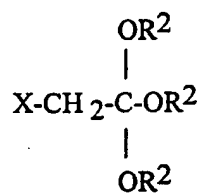
with an alkali metal in ammonia or higher order amine in the presence of a solvent to afford in situ the compound of Formula VI



VI

Step (b) treating the compound of Formula VI with a compound of Formula VIII

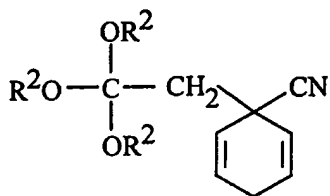
-13-



VIII

5

wherein X is halo or sulfonate and R^2 is alkyl in the presence of a solvent to afford a compound of Formula IX

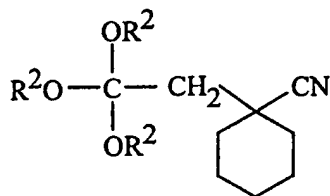


IX

wherein R^2 is alkyl;

10

Step (c) treating a compound of Formula IX with hydrogen in the presence of a catalyst and a solvent to afford a compound of Formula X

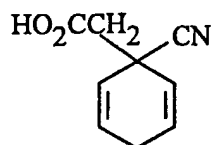


X

wherein R^2 is as defined above;

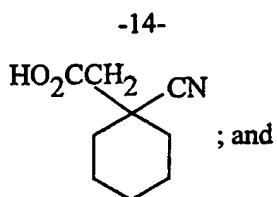
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Step (d) treating a compound of Formula IX with an acid in the presence of a solvent to afford the compound of Formula IVb



IVb

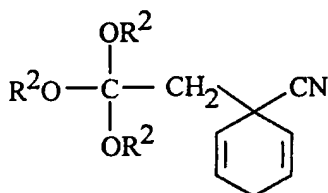
or treating a compound of Formula X with an acid in the presence of a solvent to afford the compound of Formula II



II

Step (e) treating either the compound of Formula IVb or Formula II with hydrogen in the presence of a catalyst and a solvent to afford the compound of Formula I.

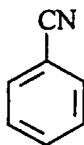
- 5 A seventh aspect of the present invention is an improved process for the preparation of a compound of Formula IX



IX

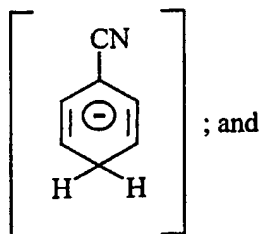
wherein R^2 is alkyl which comprises:

Step (a) treating the compound of Formula VII



VII

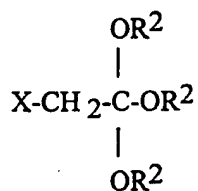
with an alkali metal in ammonia or higher order amine in the presence of a solvent to afford in situ the compound of Formula VI



VI

Step (b) treating the compound of Formula VI with a compound of Formula VIII

-15-

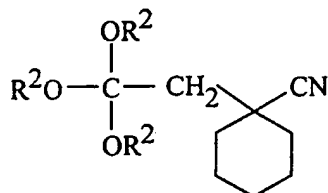


VIII

5

wherein X is halo or sulfonate and R^2 is alkyl in the presence of a solvent to afford a compound of Formula IX.

An eight aspect of the present invention is an improved process for the preparation of a compound of Formula X

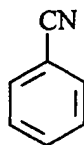


X

10

wherein R^2 is alkyl which comprises:

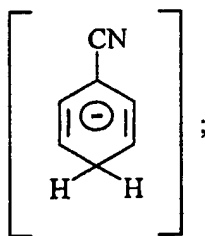
Step (a) treating the compound of Formula VII



VII

15

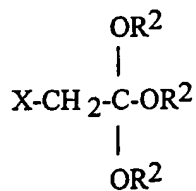
with an alkali metal in ammonia or higher order amine in the presence of a solvent to afford in situ the compound of Formula VI



VI

Step (b) treating the compound of Formula VI with a compound of Formula VIII

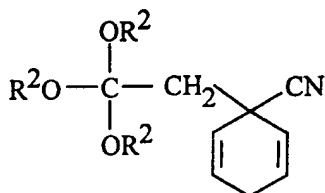
-16-



VIII

5

wherein X is halo or sulfonate and R^2 is alkyl in the presence of a solvent to afford a compound of Formula IX

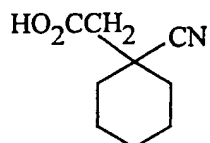


IX

wherein R^2 is alkyl; and

- 10 Step (c) treating a compound of Formula IX with hydrogen in the presence of a catalyst and a solvent to afford a compound of Formula X.

A ninth aspect of the present invention is an improved process for the preparation of the compound of Formula II



II

- 15 which comprises:

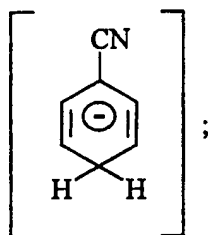
Step (a) treating the compound of Formula VII



VII

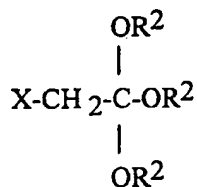
with an alkali metal in ammonia or higher order amine in the presence of a solvent to afford in situ the compound of Formula VI

-17-



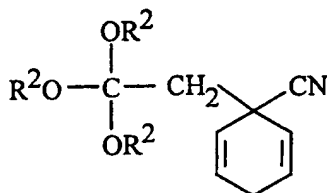
VI

Step (b) treating the compound of Formula VI with a compound of Formula VIII



VIII

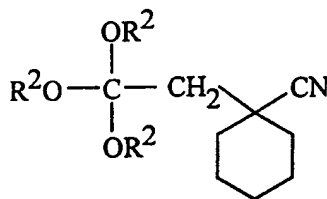
wherein X is halo or sulfonate and R² is alkyl in the presence of a solvent to afford a compound of Formula IX



IX

wherein R² is alkyl;

Step (c) treating a compound of Formula IX with hydrogen in the presence of a catalyst and a solvent to afford a compound of Formula X



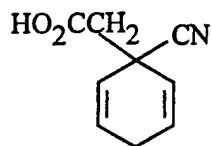
X

wherein R² is as defined above; and

Step (d) treating a compound of Formula X with an acid in the presence of a solvent to afford the compound of Formula II.

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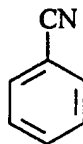
A tenth aspect of the present invention is an improved process for the preparation of the compound of Formula IVb



IVb

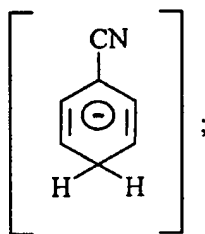
which comprises:

- 5 Step (a) treating the compound of Formula VII



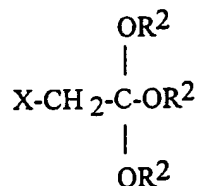
VII

with an alkali metal in ammonia or higher order amine in the presence of a solvent to afford in situ the compound of Formula VI



VI

- 10 Step (b) treating the compound of Formula VI with a compound of Formula VIII

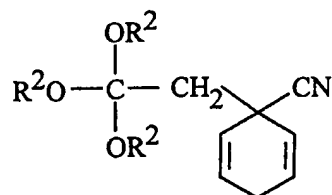


VIII

15

wherein X is halo or sulfonate and R² is alkyl in the presence of a solvent to afford a compound of Formula IX

-19-

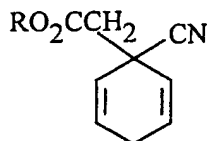


IX

wherein R^2 is alkyl; and

Step (c) treating a compound of Formula IX with an acid in the presence of a solvent to afford the compound of Formula IVb

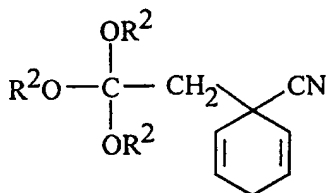
- 5 An eleventh aspect of the present invention is a novel compound of Formula IV



IV

wherein R^1 is hydrogen, an alkali metal, an alkaline earth metal, ammonium, an amine cation, alkyl, or benzyl.

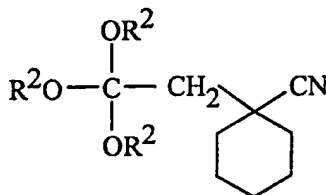
- 10 A twelfth aspect of the present invention is a novel compound of Formula IX



IX

wherein R^2 is alkyl.

- 15 A thirteenth aspect of the present invention is a novel compound of Formula X



X

-20-

wherein R² is alkyl.

DETAILED DESCRIPTION OF THE INVENTION

In this invention, the term "alkyl" means a straight or branched hydrocarbon group having from one to twelve carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tertiary-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, undecyl, dodecyl, and the like.

"Alkali metal" is a metal in Group IA of the periodic table and includes, for example, lithium, sodium, potassium, and the like.

"Alkaline-earth metal" is a metal in Group IIA of the periodic table and includes, for example, calcium, barium, strontium, magnesium, and the like.

"Halo" is halogen which is fluorine, chlorine, bromine, or iodine.

"Sulfonate" is tosyl, mesyl, phenylsulfonate, chlorophenylsulfonate, bromophenylsulfonate, methoxyphenylsulfonate, and the like.

"Higher order amine" is methylamine, dimethylamine, methylethylamine, diethylamine, and the like.

"Amine cation" is $\text{R}-\text{N}^+-\text{R}^2$ wherein R, R¹, R², R³, are the same or

$$\begin{array}{c} \text{R}^1 \\ | \\ \text{R}-\text{N}^+-\text{R}^2 \\ | \\ \text{R}^3 \end{array}$$

different and each is hydrogen, alkyl of from 1 to 8 carbon atoms, phenyl, tolyl, and the like.

The compounds of Formula I are capable of further forming both pharmaceutically acceptable acid addition and/or base salts. All of these forms are within the scope of the present invention.

Pharmaceutically acceptable acid addition salts of the compounds of Formula I include salts derived from nontoxic inorganic acids, such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids,

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hydroxy alkanolic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge S.M., et al., "Pharmaceutical Salts," Journal of Pharmaceutical Science, 1977;66:1-19).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free bases for purposes of the present invention.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge S.M., supra.).

The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acids for purposes of the present invention.

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Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

5 United States Patents Numbers 4,894,476 and 4,960,931 disclose gabapentin monohydrate and a process for producing the gabapentin monohydrate.

The following table provides a list of abbreviations and definitions thereof used in the present invention:

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DEFINITION	ABBREVIATION
Tertiary butyl alcohol	t-BuOH
Ammonia	NH ₃
Trifluoroacetic acid	TFA
Tetrahydrofuran	THF
Nitrogen	N ₂
Ethyl acetate	EtOAc
Magnesium sulfate	MgSO ₄
Dichloromethane	CH ₂ Cl ₂
Proton nuclear magnetic resonance spectroscopy	¹ H-NMR
Deuterated chloroform	CDCl ₃
Carbon nuclear magnetic resonance spectroscopy	¹³ C-NMR
Methanol	MeOH
Hydrogen	H ₂
Methyl tertiary butyl ether	MTBE
Hydrochloric acid	HCl
Palladium on charcoal	Pd/C
Ammonium hydroxide	NH ₄ OH
Deuterated methanol	CD ₃ OD
Silicon dioxide (silica)	SiO ₂
Palladium on barium sulfate	Pd/BaSO ₄
Vapor phase chromatography	VPC
Pounds per square inch	PSI
Potassium hydroxide	KOH
Sodium hydroxide	NaOH
Potassium bromide	KBr
Ethanol	EtOH
tertiary Butyl	t-Bu
Benzyl	Bn
Refractive index high performance liquid chromatography	RI HPLC
Infrared spectroscopy	IR

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DEFINITION	ABBREVIATION
Deuterium oxide	D ₂ O
Water	H ₂ O
Thin layer chromatography	TLC

Preferred compounds of Formula IV prepared by the improved process of the first aspect of the present invention are:

(1-Cyanocyclohexa-2,5-dienyl)acetic acid ethyl ester;
 (1-Cyanocyclohexa-2,5-dienyl)acetic acid;
 5 (1-Cyanocyclohexa-2,5-dienyl)acetic acid benzyl ester; and
 (1-Cyanocyclohexa-2,5-dienyl)acetic acid t-butyl ester;
 or a pharmaceutically acceptable salt thereof.

Preferred compounds of Formula IX prepared by the improved process of the fifth aspect of the present invention are:

10 1-(2,2,2-Trimethoxy-ethyl)-cyclohexa-2,5-dienecarbonitrile;
 1-(2,2,2-Triethoxy-ethyl)-cyclohexa-2,5-dienecarbonitrile; and
 1-(2,2,2-Triisopropoxy-ethyl)-cyclohexa-2,5-dienecarbonitrile.

Preferred compounds of Formula X prepared by the improved process of the fifth aspect of the present invention are:

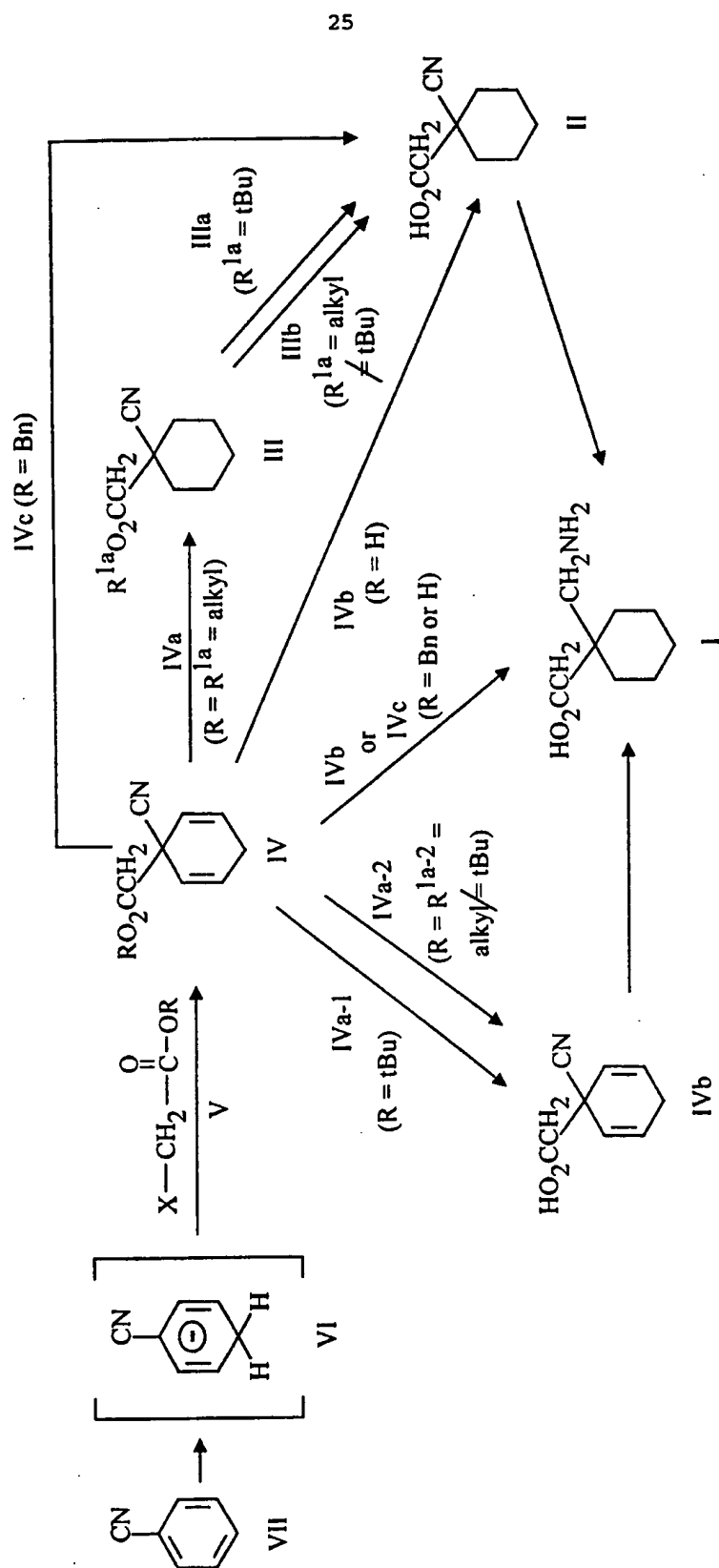
15 1-(2,2,2-Trimethoxy-ethyl)-cyclohexanecarbonitrile;
 1-(2,2,2-Triethoxy-ethyl)-cyclohexanecarbonitrile; and
 1-(2,2,2-Triisopropoxy-ethyl)-cyclohexanecarbonitrile.

As previously described, the compound of Formula I is useful for the treatment of certain forms of epilepsy, faintness attacks, hypokinesia, and cranial
 20 trauma.

The process of the present invention in its first aspect is a new, improved, economical, and commercially feasible method for preparing the compound of Formula I. Furthermore, the process can be carried out in a two-pot procedure.

The process of the present invention in its first aspect is outlined in
 25 Scheme 1.

SCHEME 1



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A compound of Formula IV is prepared from benzonitrile (VII) using a Birch reduction, i.e., dissolving metal reduction methodology followed by subsequent alkylation of the anionic intermediate (VI) which is generated in situ.

5 The alkylation of anions generated in Birch reductions is an established methodology (see "Organic Reactions", ed. Paquette L.A., et al., John Wiley & Sons, New York, New York, 1992;42:1-334) in organic synthesis. However, there is only one report of the reductive alkylation of benzonitrile (Schultz A.G. and Macielag M., Journal of Organic Chemistry, 1986;51:4983). There is no disclosure of alkylation of these intermediate anions with α -halo acetic acid esters.

10 Though alkylation of nitriles has been disclosed ("Organic Reactions", ed. Dauben W.G., et al., John Wiley & Sons, New York, New York, 1984;31:1-364), the alkylation of cyclohexanecarbonitrile and cyclohexanecarbonitrile type compounds with α -halo acetic acid esters has not been reported. We have unexpectedly and surprisingly found that the Birch reduction anionic intermediate

15 (VI) is successfully alkylated with α -haloacetic acid and α -haloacetic acid esters in high yields.

Thus, a solution of benzonitrile in a solvent such as, for example, an alcohol such as tertiary butyl alcohol, ethanol, isopropyl alcohol, tetrahydrofuran, diethyl ether, methyl tertiary butyl ether (MTBE) and the like is treated with an

20 alkali metal such as, for example, lithium, sodium, potassium, and the like an amine such as, for example, ammonia and the like at about -78°C to about -33°C for about 0.5 to about 8 hours to generate in situ the anionic intermediate (VI) followed by subsequent treatment with a compound of Formula V wherein X is halo or sulfonate and R is hydrogen, an alkali metal, an alkaline earth metal,

25 ammonium, an amine cation, alkyl, or benzyl to afford a compound of Formula IV wherein R is hydrogen, alkyl, or benzyl. Preferably, the reaction is carried out with lithium in ammonia in tertiary butyl alcohol and tetrahydrofuran.

A compound of Formula IVa wherein R (R^{1a}) is alkyl is treated with hydrogen in the presence of a catalyst such as, for example, rhodium on carbon

30 containing palladium, rhodium on carbon containing platinum, rhodium on calcium carbonate containing palladium, rhodium on alumina containing palladium, palladium on carbon, palladium on carbon in the presence of a mineral

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acid, Raney nickel, and Raney cobalt and the like and a solvent such as, for example, methanol and the like to afford a compound of Formula III wherein R^{1a} is alkyl. Preferably, the reaction is carried out with palladium on charcoal and methanol.

5 A compound of Formula IIIa (R^{1a} is tertiary butyl [t-Bu]) is treated with an acid such as, for example, hydrochloric acid, hydrobromic acid, trifluoroacetic acid, hydrobromic acid in acetic acid, formic acid, *para* toluenesulfonic acid, and the like in a solvent such as, for example, dichloromethane, toluene, diethyl ether and the like to afford the compound of Formula II. Preferably, the reaction is
10 carried out with trifluoroacetic acid in dichloromethane.

 A compound of Formula IIIb (R^{1a} is alkyl excluding tertiary butyl) is treated with an acid such as, for example, hydrochloric acid, hydrobromic acid, trifluoroacetic acid, paratoluenesulfonic acid and the like or a base such as, for example, an alkali metal hydroxide such as sodium hydroxide, potassium
15 hydroxide and the like or an alkaline earth metal hydroxide, such as calcium hydroxide and the like in a solvent such as, for example, water and/or an alcohol such as methanol, ethanol and the like to afford the compound of Formula II. Preferably, the reaction is carried out with potassium hydroxide in ethanol.

 A compound of Formula IVc (R is benzyl [Bn]) is treated with hydrogen
20 in the presence of a catalyst using the conditions previously described for preparing a compound of Formula III from a compound of Formula IVa to afford the compound of Formula II.

 The compound of Formula IVa-1 (R¹ is t-Bu) is treated with an acid in the presence of a solvent using the conditions previously described for preparing a
25 compound of Formula II from the compound of Formula IIIa to afford the compound of Formula IVb.

 The compound of Formula IVa-2 (R¹ is alkyl excluding t-Bu) is treated with an acid or base in the presence of a solvent using the conditions previously described for preparing the compound of Formula II from a compound of
30 Formula IIIb to afford the compound of Formula IVb.

 The compound of Formula IVb is treated with hydrogen in the presence of a catalyst using the conditions previously described for preparing a compound of

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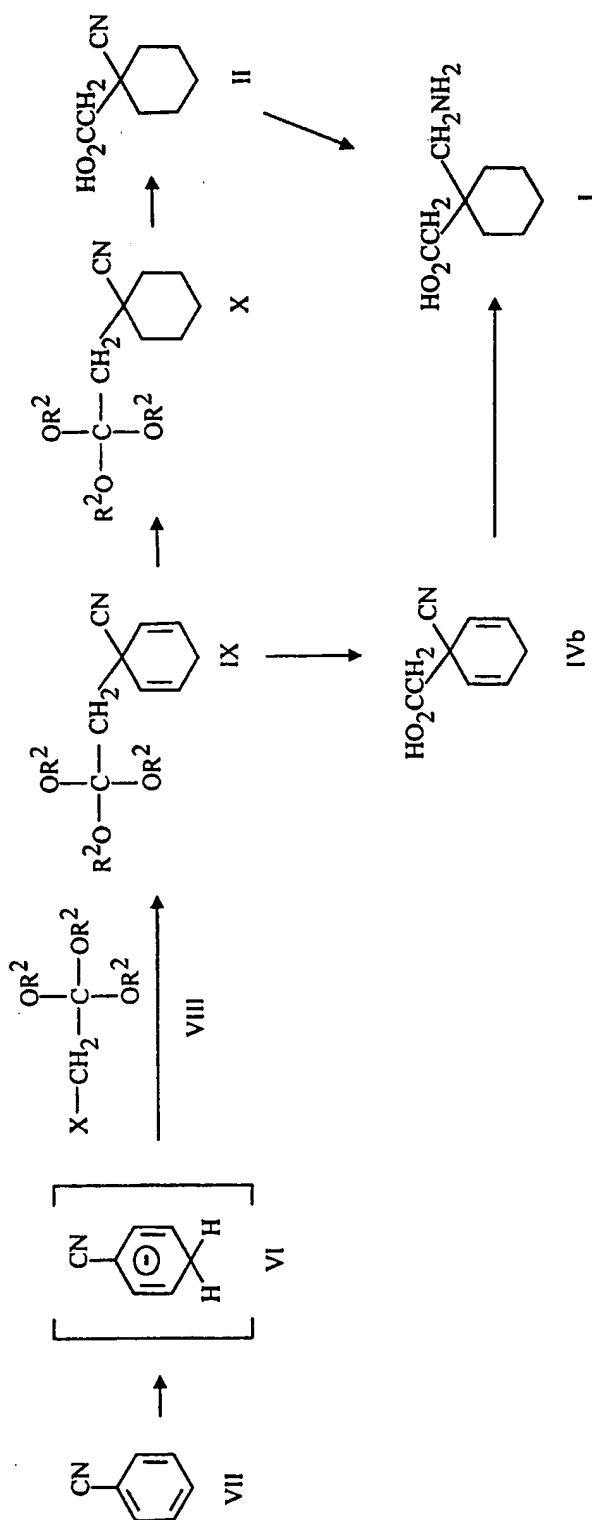
Formula III from a compound of Formula IVa to afford the compound of Formula II.

5 The compound of Formula IVb, or the compound of Formula IVc, or the compound of Formula II is treated with hydrogen in the presence of a catalyst and a solvent using the conditions previously described for preparing a compound of Formula III from a compound of Formula IVa to afford the compound of Formula I.

10 The process of the present invention in its fifth aspect is a new, improved, economical, and commercially feasible method for preparing the compound of Formula I. The process of the present invention in its fifth aspect is outlined in Scheme 2.

29

SCHEME 2



-30-

Thus, the anionic intermediate (VI) is generated in situ as described above followed by subsequent treatment with a compound of Formula VIII wherein X is halo or sulfonate and R² is alkyl using the conditions previously described for preparing a compound of Formula IV from the compound of Formula VI to afford a compound of Formula IX wherein R² is as defined above.

A compound of Formula IX is treated with hydrogen in the presence of a catalyst and a solvent using the conditions previously described for preparing a compound of Formula III from a compound of Formula IVa to afford a compound of Formula X wherein R² is as defined above.

A compound of Formula IX is treated with an acid such as, for example, formic acid, acetic acid, hydrochloric acid, hydrobromic acid, trifluoroacetic acid, *para* toluenesulfonic acid and the like in a solvent such as, for example, dichloromethane, toluene, tetrahydrofuran, diethyl ether and the like to afford the compound of Formula IVb. Preferably, the reaction is carried out with hydrochloric acid in dichloromethane.

A compound of Formula X is treated with an acid in a solvent using the conditions previously described for preparing the compound of Formula IVb from a compound of Formula IX to afford the compound of Formula II.

The compound of Formula IVb or Formula II is treated with hydrogen in the presence of a catalyst and a solvent using the conditions previously described for preparing a compound of Formula III from a compound of Formula IVa to afford the compound of Formula I.

Compounds of Formula V and Formula VIII are either known or capable of being prepared by methods known in the art.

The following nonlimiting examples illustrate the inventors' preferred method for preparing the compound of the invention.

EXAMPLE 1

1-(Aminomethyl)-cyclohexanecetic acid

METHOD A

Step A: Preparation of (1-Cyanocyclohexa-2,5-dienyl)acetic acid ethyl ester

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Lithium (0.17 g, 24 mmol) was added in portions to a solution of benzonitrile (0.99 mL, 1.0 g, 9.7 mmol) and t-BuOH (0.93 mL, 0.72 g, 9.7 mmol) in NH₃ (50 mL) and THF (10 mL) under N₂ at -78°C. After 10 minutes, ethyl bromoacetate (2.2 mL, 3.3 g, 20 mmol) was added dropwise. After 1 hour, ammonium chloride (4.0 g, 75 mmol) was added in portions. The reaction mixture was slowly warmed to room temperature while the NH₃ was removed with a stream of N₂. Water (25 mL) was added, and the mixture extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO₄), and concentrated under reduced pressure. Flash chromatography (SiO₂, CH₂Cl₂) afforded 1.12 g (60%) of product as an oil.

¹H-NMR (CDCl₃): δ 1.28 (t, J=7.1 Hz, 3H), 2.71 (m, 4H), 4.20 (q, J=7.1 Hz, 2H), 5.82 (dt, J=1.9, 10.1 Hz, 2H), 6.01 (dt, J=3.3, 10.1 Hz, 2H);

¹³C-NMR (CDCl₃): δ 14.2, 25.7, 34.4, 45.1, 61.2, 120.5, 123.6, 128.0, 168.3;

IR (neat) 2984, 2231, 1736, 1185 cm⁻¹.

15 Step B: Preparation of (1-Cyanocyclohexyl)acetic acid ethyl ester

Added 1% Pd/C catalyst (1.67 g, 0.157 mmol) to a solution of (1-cyanocyclohexa-2,5-dienyl)acetic acid ethyl ester (3.00 g, 15.7 mmol) in MeOH (75 mL). After shaking the reaction under 20 psi H₂ at room temperature for 2 hours, the pressure was slowly released. The reaction was filtered and concentrated under reduced pressure to afford 2.89 g (94%) of product as an oil.

¹H-NMR (CDCl₃): δ 1.10-1.55 (m, 5H, inc. 1.29, t, J=7.1 Hz), 1.72 (m, 6H), 2.05-2.18 (m, 2H), 2.55 (s, 2H), 4.20 (q, J=7.1 Hz, 2H);

¹³C-NMR (CDCl₃): δ 14.3, 22.9, 25.2, 35.6, 36.7, 44.5, 61.1, 122.4, 169.1.

25 Step C: Preparation of (1-Cyanocyclohexyl)acetic acid

(1-Cyanocyclohexyl)acetic acid ethyl ester is reacted with aqueous sodium hydroxide solution using the methodology disclosed at Column 15, Method C, Step B of United States Patent 5,132,451 which is herein incorporated by reference to afford the title product.

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Step D: Preparation of 1-(Aminomethyl)-cyclohexanecarboxylic acid

(1-Cyanocyclohexyl)acetic acid is hydrogenated using the methodology disclosed at Columns 14 to 15, Method B, of United States Patent 5,132,451 to afford the title compound.

5 METHOD B**Step A: Preparation of (1-Cyanocyclohexa-2,5-dienyl)acetic acid**

Lithium (0.87 g, 125 mmol) was added in portions to a stirred solution of benzonitrile (5.1 mL, 5.2 g, 50 mmol) and t-BuOH (4.8 mL, 3.7 g, 50 mmol) in THF (5 mL) and NH₃ (25 mL). After stirring at -78°C for 30 minutes, a solution
10 of bromoacetic acid ammonium salt (prepared by mixing bromoacetic acid [13.90 g, 100.0 mmol], THF (15 mL), and NH₃ (50 mL) at -78°C and stirring for 1.5 hours) was added dropwise to the reaction. After stirring at -78°C for 1 hour, ammonium chloride (20.9 g, 391 mmol) was added in portions. The reaction mixture was slowly warmed to room temperature while the NH₃ was removed
15 with a stream of N₂. Water (75 mL) was added, and the mixture extracted with MTBE (3 × 50 mL). The stirred aqueous layer was cooled to 0-5°C, acidified to pH=1 with 37% HCl, and extracted with MTBE (3 × 50 mL). The combined organic extracts of the acidified aqueous layer were dried (MgSO₄) and concentrated under reduced pressure to afford 2.49 g (31%) of product as a white
20 solid.

¹H-NMR (CDCl₃): δ 2.72 (m, 2H), 2.78 (s, 2H), 5.84 (dt, J=1.9, 10.2 Hz, 2H), 6.03 (dt, J=3.3, 10.1 Hz, 2H), 10.41 (broad s, 1H);

¹³C-NMR (CDCl₃): δ 25.7, 34.2, 44.9, 120.5, 123.4, 128.4, 174.1;

IR (KBr) 3051, 2915, 2235, 1719, 1248 cm⁻¹.

25 Step B: Preparation of (1-Cyanocyclohexyl)acetic acid

Added 5% Pd/C catalyst (0.65 g, 0.31 mmol) to a solution of (1-cyanocyclohexa-2,5-dienyl)acetic acid (0.50 g, 3.1 mmol) and 28% NH₄OH (42.5 μL, 38.3 μg, 0.31 mmol) in MeOH (15 mL). After shaking the reaction mixture under 50 psi H₂ at room temperature for 1 hour, the pressure was slowly

-33-

released. The reaction was filtered and concentrated under reduced pressure to afford 0.48 g (94%) of crude product.

$^1\text{H-NMR}$ (CD_3OD): δ 1.03-1.59 (m, 7H, theo. 3H), 1.59-1.86 (m, 4H, theo. 5H), 1.96-2.12 (m, 2H), 2.47 (s, 2H), 4.86 (s, 4H, theo. 1H);

5 RI HPLC 63% area.

Step C: Preparation of 1-(Aminomethyl)-cyclohexaneacetic acid

The title compound is prepared as described in Method A, Step D.

METHOD C

Step A: Preparation of (1-Cyanocyclohexa-2,5-dienyl)acetic acid benzyl ester

10 Lithium (0.17 g, 24 mmol) was added in portions to a stirred solution of benzonitrile (0.99 mL, 1.0 g, 9.7 mmol) and t-BuOH (0.93 mL, 0.72 g, 9.7 mmol) in NH_3 (50 mL) and THF (10 mL) under N_2 at -78°C . After stirring for 15 minutes, benzyl-2-bromoacetate (3.1 mL, 4.5 g, 20 mmol) was added dropwise. After 1 hour, ammonium chloride (4.0 g, 75 mmol) was added in
15 portions. The reaction mixture was slowly warmed to room temperature while the NH_3 was removed with a stream of N_2 . Water (25 mL) was added, and the mixture extracted with EtOAc (3×5 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO_4), and concentrated under reduced pressure. Flash chromatography (SiO_2 , 1:1-3:1 CH_2Cl_2 :hexane) afforded 1.79 g
20 (73%) of product as an oil.

$^1\text{H-NMR}$ (CDCl_3): δ 2.60-2.71 (m, 2H), 2.77 (s, 2H), 5.17 (s, 2H), 5.79 (dt, $J=1.8, 10.0$ Hz, 2H), 5.97 (dt, $J=3.3, 9.8$ Hz, 2H), 7.37 (m, 5H);

$^{13}\text{C-NMR}$ (CDCl_3): δ 25.6, 34.4, 45.0, 67.0, 120.5, 123.4, 128.1, 128.5, 128.6, 128.9, 135.5, 168.1;

25 IR (neat) 3035, 2233, 1738, 1170 cm^{-1} .

Step B: Preparation of (1-Cyanocyclohexyl)acetic acid

Added 5% Pd/ BaSO_4 catalyst (9.0 mg, 4.2 μmol) to a solution of (1-cyanocyclohexa-2,5-dienyl)acetic acid benzyl ester (1.00 g, 3.95 mmol) in

-34-

MeOH (20 mL). After stirring the reaction mixture under an atmosphere of H₂ at 0°C for 0.5 hour and room temperature for 1.5 hours, additional 5%

Pd/BaSO₄ (75.8 mg, 35.6 μmol) was added. After stirring the reaction mixture under an atmosphere of H₂ at 0°C for 1 hour and room temperature for

5 19.5 hours, the reaction was filtered and concentrated under reduced pressure to afford 0.56 g (87%) of crude oil.

¹H-NMR (CD₃OD) complex mix showing majority of product;

VPC assay 43% area;

RI HPLC assay 40% area.

10 Step C: Preparation of 1-(Aminomethyl)-cyclohexanecarboxylic acid
(1-Cyanocyclohexyl)acetic acid is hydrogenated according to the procedure of Method A, Step D to afford the title compound.

METHOD D

Step A: Preparation of (1-Cyanocyclohexa-2,5-dienyl)acetic acid *t*-butyl ester

15 Lithium (1.73 g, 249 mmol) was added in portions to a stirred solution of benzonitrile (10.2 mL, 10.3 g, 99.9 mmol) and *t*-BuOH (9.6 mL, 7.4 g, 100 mmol) in NH₃ (50 mL) and THF (10 mL) under N₂ at -78°C. After stirring for 25 minutes, *t*-butyl bromoacetate (29.5 mL, 39.0 g, 200 mmol) was added dropwise. After 1 hour, ammonium chloride (41.8 g, 781 mmol) was added in
20 portions. The reaction mixture was slowly warmed to room temperature while the NH₃ was removed with a stream of N₂. Water (125 mL) was added and the mixture extracted with MTBE (3 × 50 mL). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. Flash chromatography (SiO₂, CH₂Cl₂-1:14 MTBE:CH₂Cl₂) afforded 16.0 g (73%) of product as an oil.

25 ¹H-NMR (CDCl₃): δ 1.48 (s, 9H), 2.61 (s, 2H), 2.67-2.76 (m, 2H), 5.80 (dt, J=1.9, 10.3 Hz, 2H), 5.99 (dt, J=3.3, 10.2 Hz, 2H);
¹³C-NMR (CDCl₃): δ 25.6, 28.1, 34.5, 46.3, 82.0, 120.6, 123.8, 127.7, 167.5;
IR (neat) 2980, 2232, 1729, 1153 cm⁻¹.

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Step B: Preparation of (1-Cyanocyclohexyl)acetic acid t-butyl ester

Added 5% Pd/C, 50% H₂O catalyst (94.0 mg, 22.1 μ mol) to a solution of (1-cyanocyclohexa-2,5-dienyl)acetic acid t-butyl ester (0.50 g, 2.3 mmol) in MeOH (10 mL). After shaking the reaction mixture under 20 psi H₂ at room temperature for 18.5 hours, the pressure was slowly released. The reaction was filtered and concentrated under reduced pressure. Flash chromatography (SiO₂, 1:3 hexane:CH₂Cl₂-100% CH₂Cl₂) afforded 0.29 g (56%) of product as an oil. ¹H-NMR (CDCl₃): δ 1.10-1.45 (m, 4H), 1.49 (s, 9H), 1.60-1.89 (m, 4H), 1.95-2.21 (m, 2H), 2.45 (s, 2H); ¹³C-NMR (CDCl₃): δ 22.9, 25.2, 28.2, 35.7, 36.8, 45.7, 81.9, 122.6, 168.6; IR (neat) 2935, 2234, 1729, 1368, 1149 cm⁻¹.

Step C: Preparation of (1-Cyanocyclohexyl)acetic acid

To a solution of 2.4 mL (2.4 g, 22 mmol) of anisole in 50 mL of trifluoroacetic acid is added 5.00 g (22.4 mmol) of (1-cyanocyclohexyl)acetic acid, *t*-butyl ester. The reaction is monitored (TLC) for the loss of starting material and when the reaction is complete it is concentrated under reduced pressure. Water (~10 mL) is added to the residue and the mixture is adjusted to pH = 10-12 with base (NaOH). The basic aqueous layer is extracted with a suitable organic solvent (EtOAc) to remove impurities. The aqueous layer is acidified with acid (HCl) to pH = 0-4 and extracted with a suitable solvent (EtOAc). The combined organic extracts of the acidified aqueous layer are dried and concentrated under reduced pressure to afford the product.

Step D: Preparation of 1-(Aminomethyl)cyclohexaneacetic acid

(1-Cyanocyclohexyl)acetic acid is hydrogenated according to the procedure of Method A, Step D to afford the title compound.

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METHOD E

Step A: Preparation of (1-Cyanocyclohexa-2,5-dienyl)acetic acidMethod a:

Added dropwise a solution of KOH (1.73 M, 5.0 mL, 8.7 mmol) in
5 1:4 H₂O:2B EtOH to a stirred solution of (1-cyanocyclohexa-2,5-dienyl)acetic
acid ethyl ester (3.00 g, 15.7 mmol) in 2B EtOH (15 mL) at 0°C. After stirring for
1 hour, a solution of KOH (1.73 M, 5.0 mL, 8.7 mmol) in 1:4 H₂O:2B EtOH was
added dropwise. After stirring for 2.5 hours, the reaction was concentrated under
reduced pressure. Water (5 mL) was added, and the mixture was extracted with
10 CH₂Cl₂ (3 × 10 mL). The aqueous layer was cooled to 5°C and acidified to
pH=3 with 37% HCl (1.1 mL, 13.4 mmol). The solids were filtered, washed with
H₂O (pH=5), and dried under vacuum at room temperature for 16 hours to afford
1.57 g (61%) of the product as a solid.
¹H-NMR (CDCl₃): δ 2.73 (m, 2H), 2.78 (s, 2H), 5.83 (dt, J=1.9, 10.3 Hz, 2H),
15 6.03 (dt, J=3.4, 10.4 Hz, 2H), 9.27 (broad s, 1H);
¹³C-NMR: δ 25.8, 34.3, 44.8, 120.5, 123.4, 128.4, 173.8.

Method b

To a solution of 2.5 mL (2.5 g, 23 mmol) of anisole in 50 mL of
trifluoroacetic acid is added 5.00 g (22.8 mmol) of (1-cyanocyclohexa-2,5-dienyl)
20 acetic acid, *t*-butyl ester. The reaction is monitored (TLC) for the loss of starting
material and when the reaction is complete it is concentrated under reduced
pressure. Water (~10 mL) is added to residue and the mixture is adjusted to
pH = 10-12 base (NaOH). The basic aqueous layer is extracted with a suitable
organic solvent (EtOAc) to remove impurities. The aqueous layer is acidified with
25 acid (HCl) to pH = 0.4 and extracted with a suitable solvent (EtOAc). The
combined organic extracts of the acidified aqueous layer are dried and
concentrated under reduced pressure to afford the product.

Step B: Preparation of 1-(Aminomethyl)cyclohexaneacetic acid

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Added 5% Pd/C catalyst (0.33 g, 0.16 mmol) to a solution of (1-cyanocyclohexa-2,5-dienyl)acetic acid (0.25 g, 1.5 mmol) and 28% NH₄OH (70 μ L, 63 μ g, 0.50 mmol) in MeOH (20 mL). After shaking the reaction mixture under 50 psi H₂ at 50°C for 3.5 hours, the pressure was slowly released, and the reaction was cooled to room temperature. The reaction was filtered and concentrated under reduced pressure to afford 0.27 g (102%) of crude product.

¹H-NMR (D₂O): δ 1.46 (m, 11H, theo. 10H), 2.43 (s, 2H), 3.00 (s, 2H), 4.78 (s, 4H, theo. 3H);

¹³C-NMR (D₂O): δ 20.5, 24.8, 33.0, 33.8, 45.4, 47.8, 179.8.

10 METHOD F

Preparation of 1-(Aminomethyl)cyclohexaneacetic acid

Added 5% Pd/C catalyst (0.84 g, 0.40 mmol) to a solution of (1-cyanocyclohexa-2,5-dienyl)acetic acid benzyl ester (1.00 g, 3.95 mmol) and 28% NH₄OH (0.55 mL, 0.50 g, 4.0 mmol) in MeOH (20 mL). After shaking the reaction mixture under 50 psi H₂ at 50°C for 18 hours, the pressure was slowly released, and the reaction was cooled to room temperature. The reaction was filtered and concentrated under reduced pressure to afford 0.63 g (93%) of crude product.

¹H-NMR (CD₃OD): δ 1.51 (m, 11H, theo. 10H), 2.45 (s, 2H), 2.89 (s, 2H), 4.94 (s, 9H, theo. 3H);

RI HPLC 68% area.

METHOD G

Step A: Preparation of (1-Cyanocyclohexa-2,5-dienyl)acetic acid

The title compound is prepared as described in Method B, Step A.

25 Step B: Preparation of 1-(Aminomethyl)cyclohexaneacetic acid

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The title compound is prepared as described in Method E, Step B.

METHOD H

Step A: Preparation of (1-Cyanocyclohexa-2,5-dienyl)acetic acid ethyl ester

The title compound is prepared as described in Method A, Step A.

5 Step B: Preparation of (1-Cyanocyclohexa-2,5-dienyl)acetic acid

The title compound is prepared as described in Method E, Step A.

Step C: Preparation of (1-Cyanocyclohexyl)acetic acid

The title compound is prepared as described in Method B, Step B.

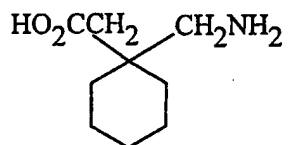
Step D: Preparation of 1-(Aminomethyl)cyclohexaneacetic acid

10 The title compound is prepared as described in Method A, Step D.

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CLAIMS

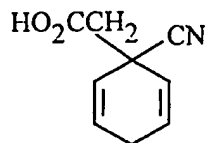
1. A process for the preparation of the compound of Formula I



I

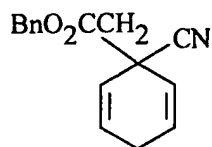
which comprises:

- 5 treating either the compound of Formula IVb



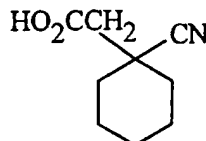
IVb

or the compound of Formula IVc



IVc

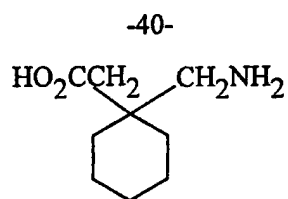
or the compound of Formula II



II

10 with hydrogen in the presence of a catalyst and a solvent to afford the compound of Formula I.

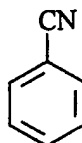
2. A process for the preparation of the compound of Formula I



I

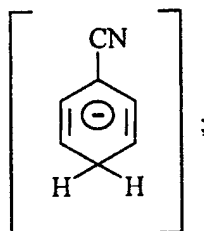
which comprises:

Step (a) treating the compound of Formula VII



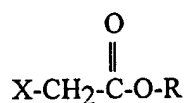
VII

- 5 with an alkali metal in ammonia or higher order amine in the presence of a solvent to afford in situ the compound of Formula VI



VI

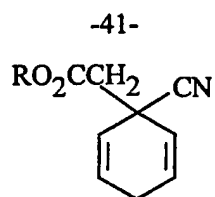
Step (b) treating the compound of Formula VI with a compound of Formula V



V

wherein X is halo or sulfonate and R is hydrogen, an alkali metal, an alkaline earth metal, ammonium, an amine cation, alkyl, or benzyl in the presence of a solvent to afford a compound of Formula IV

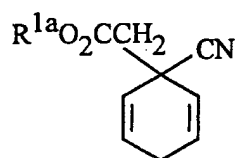
15



IV

wherein R is as defined above;

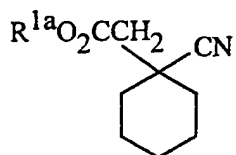
Step (c) treating a compound of Formula IVa



IVa

5

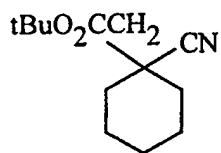
wherein R^{1a} is alkyl with hydrogen in the presence of a catalyst and a solvent to afford a compound of Formula III



III

wherein R^{1a} is as defined above;

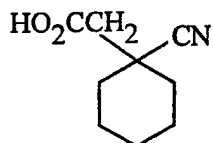
Step (d) treating the compound of Formula IIIa



IIIa

10

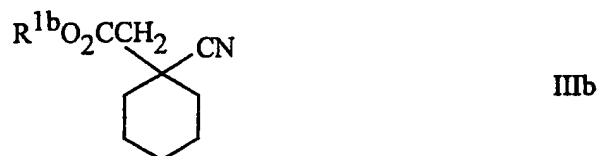
with an acid in a solvent to afford the compound of Formula II



II

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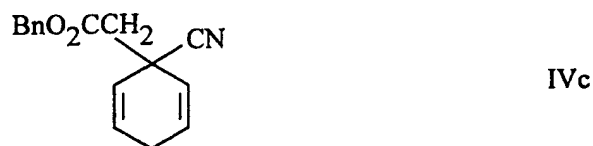
or treating a compound of Formula IIIb



wherein R^{1b} is alkyl excluding tertiary butyl with an acid or base in a solvent to afford the compound of Formula II or treating the compound of Formula IVb



with hydrogen in the presence of a catalyst and a solvent to afford the compound of Formula II or treating the compound of Formula IVc



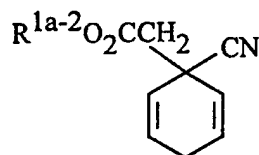
with hydrogen in the presence of a catalyst and a solvent to afford the compound of Formula II;

Step (e) treating the compound of Formula IVa-1



with an acid in a solvent to afford the compound of Formula IVb
or treating a compound of Formula IVa-2

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IVa-2

wherein R^{1a-2} is alkyl excluding tertiary butyl with an acid or base in a solvent to afford the compound of Formula IVb; and

Step (f) treating either the compound of Formula IVb

5 or the compound of Formula IVc

or the compound of Formula II with hydrogen in the presence of a catalyst and a solvent to afford the compound of Formula I.

3. A process according to Claim 2 wherein the alkali metal in Step (a) is selected from the group consisting of: lithium, sodium, and potassium.
- 10 4. A process according to Claim 3 wherein the alkali metal is lithium.
5. A process according to Claim 2 wherein the solvent in Step (a) is selected from the group consisting of: ethanol, isopropyl alcohol, tertiary butyl alcohol, tetrahydrofuran, diethyl ether, and methyl tertiary butyl ether.
6. A process according to Claim 5 wherein the solvent is a mixture of tertiary butyl alcohol and tetrahydrofuran.
- 15 7. A process according to Claim 2 wherein the higher order amine in Step (a) is selected from the group of: methylamine, dimethylamine, methylethylamine, and diethylamine.
8. A process according to Claim 2 wherein the compound of Formula V in
- 20 Step (b) is selected from the group consisting of: ethyl bromoacetate, ethyl chloroacetate, bromoacetic acid, chloroacetic acid, bromoacetic acid ammonium salt, chloroacetic acid ammonium salt, benzyl-2-bromoacetate, benzyl 2-chloroacetate, t-butyl bromoacetate, and t-butyl chloroacetate.

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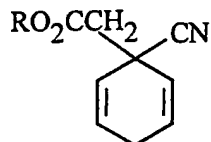
9. A process according to Claim 2 wherein the solvent in Step (b) is a mixture of tertiary butyl alcohol and tetrahydrofuran.
10. A process according to Claim 2 wherein the catalyst in Step (c) is selected from the group consisting of: rhodium on carbon containing palladium,
5 rhodium on carbon containing platinum, rhodium on calcium carbonate containing palladium, rhodium on alumina containing palladium, palladium on carbon, palladium on carbon in the presence of a mineral acid, Raney nickel, and Raney cobalt.
11. A process according to Claim 10 wherein the catalyst is palladium on
10 carbon.
12. A process according to Claim 2 wherein the solvent in Step (c) is methanol.
13. A process according to Claim 2 wherein the acid in Step (d) is selected from the group consisting of: hydrochloric acid, hydrobromic acid,
15 trifluoroacetic acid, hydrobromic acid in acetic acid, formic acid, and *para* toluenesulfonic acid.
14. A process according to Claim 13 wherein the acid is trifluoroacetic acid.
15. A process according to Claim 2 wherein the solvent in Step (d) is selected from the group consisting of: dichloromethane, toluene, and diethyl ether.
- 20 16. A process according to Claim 15 wherein the solvent is dichloromethane.
17. A process according to Claim 2 wherein the base in Step (d) is selected from the group consisting of: an alkali metal hydroxide and an alkaline earth metal hydroxide.
- 25 18. A process according to Claim 17 wherein the base is an alkali metal hydroxide.

-45-

19. A process according to Claim 18 wherein the base is potassium hydroxide.
20. A process according to Claim 2 wherein the acid in Step (e) is selected from the group consisting of: hydrochloric acid, hydrobromic acid, trifluoroacetic acid, hydrobromic acid in acetic acid, and *para* toluenesulfonic acid.
21. A process according to Claim 20 wherein the acid is trifluoroacetic acid.
22. A process according to Claim 2 wherein the solvent in Step (e) is selected from the group consisting of: dichloromethane, toluene, and diethyl ether.
23. A process according to Claim 22 wherein the solvent is dichloromethane.
24. A process according to Claim 2 wherein the base in Step (e) is selected from the group consisting of: an alkali metal hydroxide and an alkaline earth metal hydroxide.
25. A process according to Claim 24 wherein the base is an alkali metal hydroxide.
26. A process according to Claim 2 wherein the catalyst in Step (f) is selected from the group consisting of: rhodium on carbon containing palladium, rhodium on carbon containing platinum, rhodium on calcium carbonate containing palladium, rhodium on alumina containing palladium, palladium on carbon, palladium on carbon in the presence of a mineral acid, Raney nickel, and Raney cobalt.
27. A process according to Claim 26 wherein the catalyst is palladium on carbon.
28. A process according to Claim 2 wherein the solvent in Step (f) is methanol.

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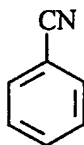
29. A process for the preparation of a compound of Formula IV



IV

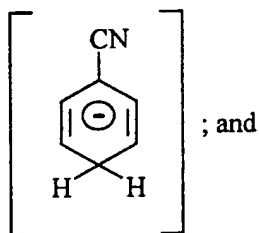
wherein R is hydrogen, an alkali metal, an alkaline earth metal, ammonium, an amine cation, alkyl, or benzyl which comprises:

- 5 Step (a) treating the compound of Formula VII



VII

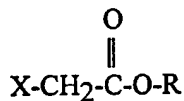
with an alkali metal in ammonia or higher order amine in the presence of a solvent to afford in situ the compound of Formula VI



; and

VI

- 10 Step (b) treating the compound of Formula VI with a compound of Formula V

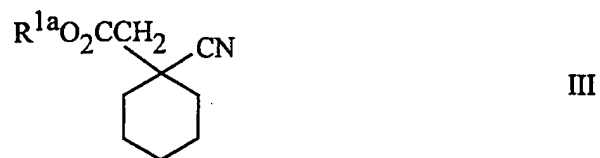


V

- 15 wherein X is halo or sulfonate and R is hydrogen, an alkali metal, an alkaline earth metal, ammonium, an amine cation, alkyl, or benzyl in the presence of a solvent to afford a compound of Formula IV.

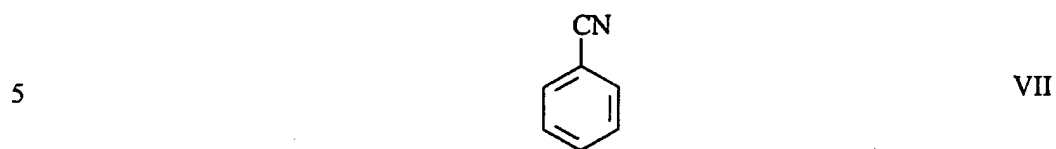
-47-

30. A process for the preparation of a compound of Formula III

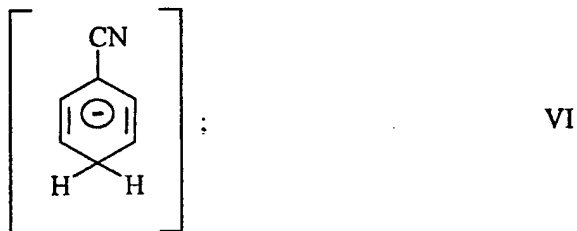


wherein R^{1a} is alkyl which comprises:

Step (a) treating the compound of Formula VII



with an alkali metal in ammonia or higher order amine in the presence of a solvent to afford in situ the compound of Formula VI

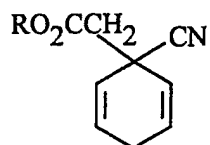


- 10 Step (b) treating the compound of Formula VI with a compound of Formula V



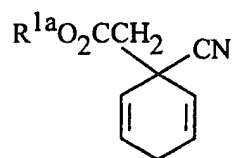
-48-

wherein X is halo or sulfonate and R is hydrogen, an alkali metal, an alkaline earth metal, ammonium, an amine cation, alkyl, or benzyl in the presence of a solvent to afford a compound of Formula IV



IV

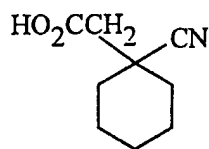
- 5 wherein R is as defined above; and
Step (c) treating a compound of Formula IVa



IVa

wherein R^{1a} is alkyl with hydrogen in the presence of a catalyst and a solvent to afford a compound of Formula III.

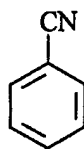
- 10 31. A process for the preparation of the compound of Formula II



II

which comprises:

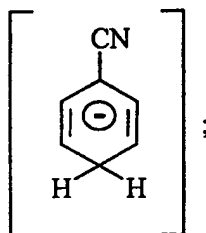
Step (a) treating the compound of Formula VII



VII

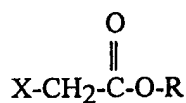
-49-

with an alkali metal in ammonia or higher order amine in the presence of a solvent to afford in situ the compound of Formula VI



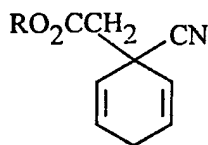
VI

Step (b) treating the compound of Formula VI with a compound of Formula V



V

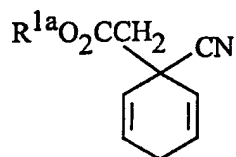
wherein X is halo or sulfonate and R is hydrogen, an alkali metal, an alkaline earth metal, ammonium, an amine cation, alkyl, or benzyl in the presence of a solvent to afford a compound of Formula IV



IV

wherein R is as defined above;

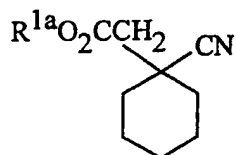
Step (c) treating a compound of Formula IVa



IVa

-50-

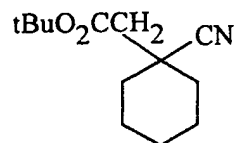
wherein R^{1a} is alkyl with hydrogen in the presence of a catalyst and a solvent to afford a compound of Formula III



III

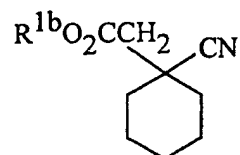
wherein R^{1a} is as defined above; and

5 Step (d) treating the compound of Formula IIIa



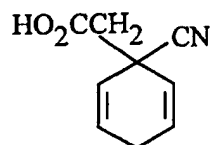
IIIa

with an acid in a solvent to afford the compound of Formula II or treating a compound of Formula IIIb



IIIb

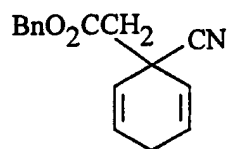
10 wherein R^{1b} is alkyl excluding tertiary butyl with an acid or base in a solvent to afford the compound of Formula II or treating the compound of Formula IVb



IVb

15 with hydrogen in the presence of a catalyst and a solvent to afford the compound of Formula II or treating the compound of Formula IVc

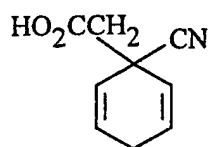
-51-



IVc

with hydrogen in the presence of a catalyst and a solvent to afford the compound of Formula II.

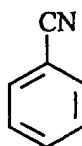
32. A process for the preparation of the compound of Formula IVb



IVb

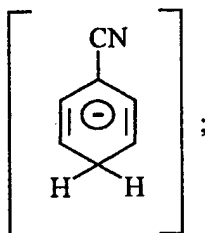
which comprises:

Step (a) treating the compound of Formula VII



VII

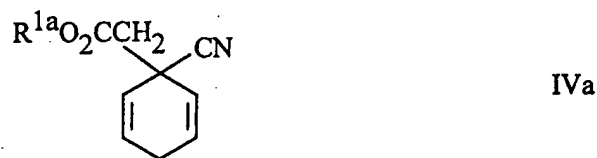
with an alkali metal in ammonia or higher order amine in the presence of a solvent to afford in situ the compound of Formula VI



Step (b) treating the compound of Formula VI with a compound of Formula Va



- 5 wherein X is halo or sulfonate and R^{1a} alkyl in the presence of a solvent to afford a compound of Formula IVa



wherein R^{1a} is as defined above; and
 Step (c) treating a compound of Formula IVa
 with an acid or base in a solvent to afford the compound of Formula IVb.

- 10 33. A compound of Formula IV

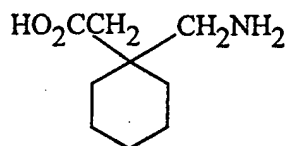


wherein R¹ is hydrogen, an alkali metal, an alkaline earth metal, ammonium, an amine cation, alkyl, or benzyl.

- 15 34. A compound selected from the group consisting of:
 (1-Cyanocyclohexa-2,5-dienyl)acetic acid ethyl ester;
 (1-Cyanocyclohexa-2,5-dienyl)acetic acid;
 (1-Cyanocyclohexa-2,5-dienyl)acetic acid benzyl ester; and
 (1-Cyanocyclohexa-2,5-dienyl)acetic acid *t*-butyl ester;
 or a pharmaceutically acceptable salt thereof.

-53-

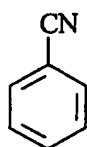
35. A process for the preparation of the compound of Formula I



I

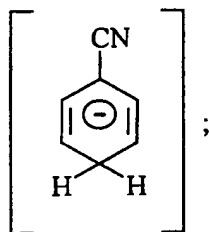
which comprises:

Step (a) treating the compound of Formula VII



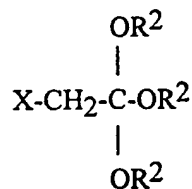
VII

with an alkali metal in ammonia or higher order amine in the presence of a solvent to afford in situ the compound of Formula VI



VI

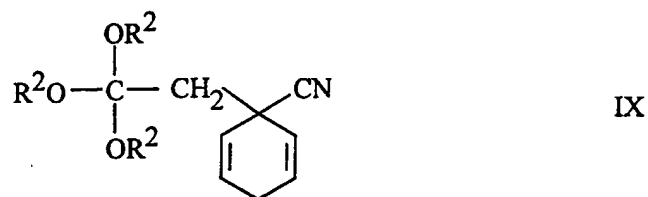
Step (b) treating the compound of Formula VI with a compound of Formula VIII



VIII

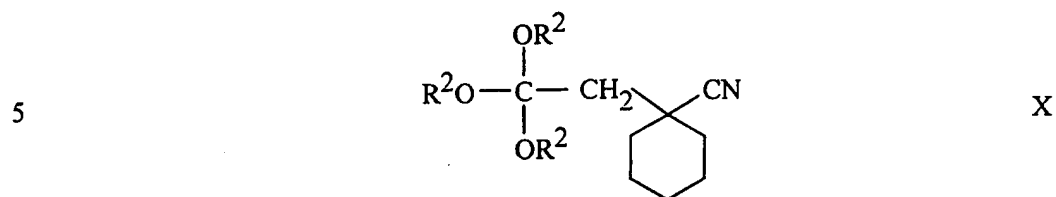
wherein X is halo or sulfonate and R² is alkyl in the presence of a solvent to afford a compound of Formula IX

-54-



wherein R^2 is alkyl;

Step (c) treating a compound of Formula IX with hydrogen in the presence of a catalyst and a solvent to afford a compound of Formula X

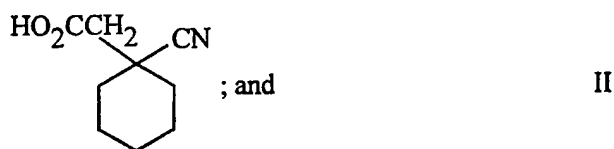


wherein R^2 is as defined above;

Step (d) treating a compound of Formula IX with an acid in the presence of a solvent to afford the compound of Formula IVb



or treating a compound of Formula X with an acid in the presence of a solvent to afford the compound of Formula II



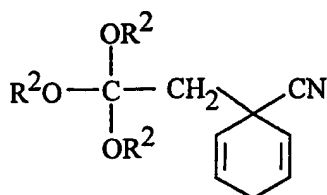
Step (e) treating either the compound of Formula IVb or Formula II with hydrogen in the presence of a catalyst and a solvent to afford the compound of Formula I.

-55-

36. A process according to Claim 35 wherein the alkali metal in Step (a) is selected from the group consisting of: lithium, sodium, and potassium.
37. A process according to Claim 36 wherein the alkali metal is lithium.
- 5 38. A process according to Claim 35 wherein the solvent in Step (a) is selected from the group consisting of: ethanol, isopropyl alcohol, tertiary butyl alcohol, tetrahydrofuran, diethyl ether, and methyl tertiary butyl ether.
39. A process according to Claim 38 wherein the solvent is a mixture of tertiary butyl alcohol and tetrahydrofuran.
- 10 40. A process according to Claim 35 wherein the solvent in Step (a) is a mixture of tertiary butyl alcohol and tetrahydrofuran.
- 15 41. A process according to Claim 35 wherein the compound of Formula VIII in Step (b) is selected from the group consisting of: 2-chloro-1,1,1-trimethoxyethane, 2-bromo-1,1,1-trimethoxyethane, 2-chloro-1,1,1-triethoxyethane, 2-bromo-1,1,1-triethoxyethane, 2-chloro-1,1,1-triisopropylethane, and 2-bromo-1,1,1-triisopropylethane.
42. A process according to Claim 35 wherein the solvent in Step (b) is a mixture of tertiary butyl alcohol and tetrahydrofuran.
- 20 43. A process according to Claim 35 wherein the catalyst in Step (c) is selected from the group consisting of: rhodium on carbon containing palladium, rhodium on carbon containing platinum, rhodium on calcium carbonate containing palladium, rhodium on alumina containing palladium, palladium on carbon, palladium on carbon in the presence of a mineral acid, Raney nickel, and Raney cobalt.
- 25 44. A process according to Claim 43 wherein the catalyst is palladium on carbon.

-56-

45. A process according to Claim 35 wherein the solvent in Step (c) is methanol.
46. A process according to Claim 35 wherein the acid in Step (d) is selected from the group consisting of: formic acid, acetic acid, hydrochloric acid, hydrobromic acid, trifluoroacetic acid, and *para* toluenesulfonic acid.
47. A process according to Claim 45 wherein the acid is hydrochloric acid.
48. A process according to Claim 45 wherein the solvent in Step (d) is dichloromethane, toluene, tetrahydrofuran, and diethyl ether.
49. A process according to Claim 48 wherein the solvent is dichloromethane.
50. A process according to Claim 45 wherein the catalyst in Step (e) is selected from the group consisting of: rhodium on carbon containing palladium, rhodium on carbon containing platinum, rhodium on calcium carbonate containing palladium, rhodium on alumina containing palladium, palladium on carbon, palladium on carbon in the presence of a mineral acid, Raney nickel, and Raney cobalt.
51. A process according to Claim 50 wherein the catalyst is palladium on carbon.
52. A process according to Claim 45 wherein the solvent in Step (e) is methanol.
53. A process for the preparation of a compound of Formula IX

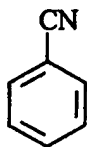


IX

-57-

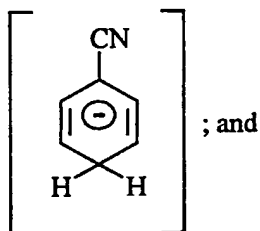
wherein R^2 is alkyl which comprises:

Step (a) treating the compound of Formula VII



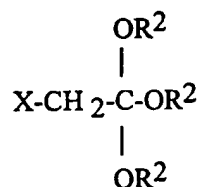
VII

with an alkali metal in ammonia or higher order amine in the presence of a solvent to afford in situ the compound of Formula VI



VI

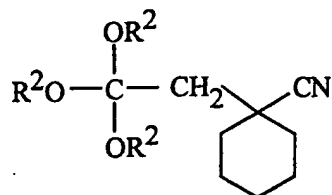
Step (b) treating the compound of Formula VI with a compound of Formula VIII



VIII

wherein X is halo or sulfonate and R^2 is alkyl in the presence of a solvent to afford a compound of Formula IX.

54. A process for the preparation of a compound of Formula X

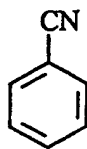


X

-58-

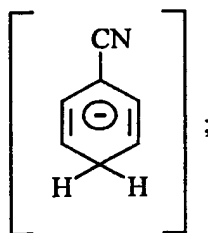
wherein R^2 is alkyl which comprises:

Step (a) treating the compound of Formula VII



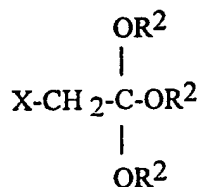
VII

with an alkali metal in ammonia or higher order amine in the presence of a solvent to afford in situ the compound of Formula VI



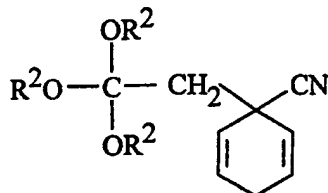
VI

Step (b) treating the compound of Formula VI with a compound of Formula VIII



VIII

wherein X is halo or sulfonate and R^2 is alkyl in the presence of a solvent to afford a compound of Formula IX



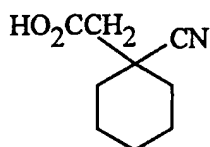
IX

wherein R^2 is alkyl; and

-59-

Step (c) treating a compound of Formula IX with hydrogen in the presence of a catalyst and a solvent to afford a compound of Formula X.

55. A process for the preparation of the compound of Formula II

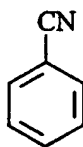


II

5

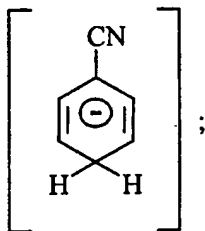
which comprises:

Step (a) treating the compound of Formula VII



VII

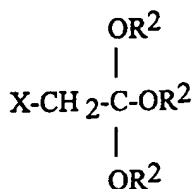
with an alkali metal in ammonia or higher order amine in the presence of a solvent to afford in situ the compound of Formula VI



VI

10

Step (b) treating the compound of Formula VI with a compound of Formula VIII

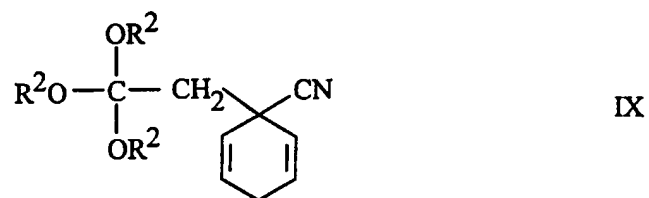


VIII

15

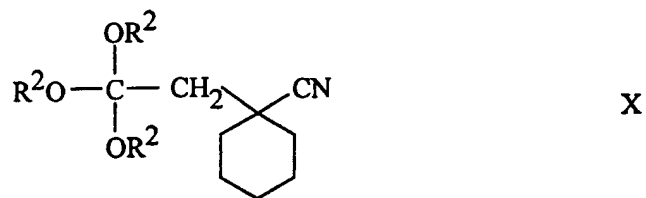
-60-

wherein X is halo or sulfonate and R² is alkyl in the presence of a solvent to afford a compound of Formula IX



wherein R² is alkyl;

- 5 Step (c) treating a compound of Formula IX with hydrogen in the presence of a catalyst and a solvent to afford a compound of Formula X



wherein R² is as defined above; and

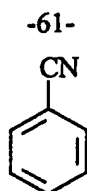
- 10 Step (d) treating a compound of Formula X with an acid in the presence of a solvent to afford the compound of Formula II.

56. A process for the preparation of the compound of Formula IVb



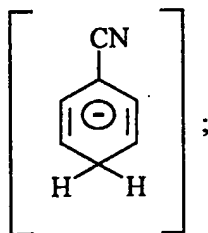
which comprises:

- Step (a) treating the compound of Formula VII



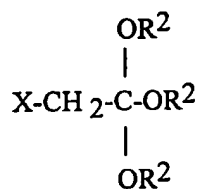
VII

with an alkali metal in ammonia or higher order amine in the presence of a solvent to afford in situ the compound of Formula VI



VI

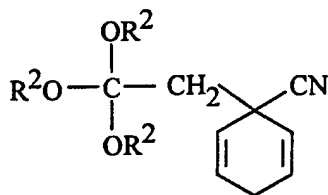
5 Step (b) treating the compound of Formula VI with a compound of Formula VIII



VIII

10

wherein X is halo or sulfonate and R^2 is alkyl in the presence of a solvent to afford a compound of Formula IX



IX

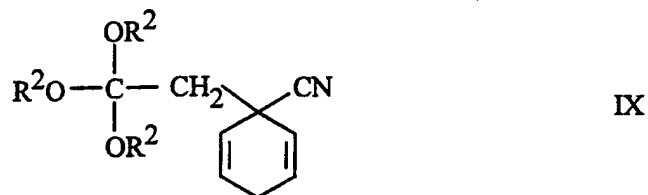
15

wherein R^2 is alkyl; and

Step (c) treating a compound of Formula IX with an acid in the presence of a solvent to afford the compound of Formula IVb.

-62-

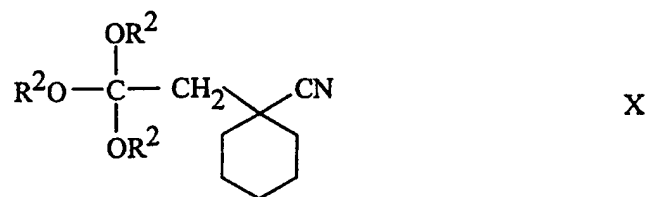
57. A compound of Formula IX



wherein R² is alkyl.

58. A compound according to Claim 57 selected from the group consisting of:
- 5 1-(2,2,2-Trimethoxy-ethyl)-cyclohexa-2,5-dienecarbonitrile;
 1-(2,2,2-Triethoxy-ethyl)-cyclohexa-2,5-dienecarbonitrile; and
 1-(2,2,2-Triisopropoxy-ethyl)-cyclohexa-2,5-dienecarbonitrile.

59. A compound of Formula X



10 wherein R² is alkyl.

60. A compound according to Claim 59 selected from the group consisting of:
- 1-(2,2,2-Trimethoxy-ethyl)-cyclohexanecarbonitrile;
 1-(2,2,2-Triethoxy-ethyl)-cyclohexanecarbonitrile; and
 1-(2,2,2-Triisopropoxy-ethyl)-cyclohexanecarbonitrile.

PCT

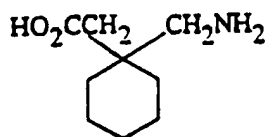
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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			(43) International Publication Date: 15 April 1999 (15.04.99)
(21) International Application Number: PCT/US98/19359 (22) International Filing Date: 16 September 1998 (16.09.98) (30) Priority Data: 60/061,383 7 October 1997 (07.10.97) US (71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): DEERING, Carl, Francis [US/US]; 2688 Kragspough Court, Holland, MI 49424 (US). MENNEN, Kenneth, Earl [US/US]; 66 W. 26th Street, Holland, MI 49423 (US). RAMAGE, Robert [GB/GB]; 26 Craigleith View, Edinburgh EH4 3JZ (GB). (74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU. ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i> (88) Date of publication of the international search report: 24 June 1999 (24.06.99)	

(54) Title: PROCESS FOR PREPARING A CYCLIC AMINO ACID ANTICONVULSANT COMPOUND



(I)

(57) Abstract

An improved process for the preparation of a cyclic amino acid of formula (I) by a novel synthesis is described where benzonitrile is treated with an alkali metal and an amine under Birch reduction conditions to generate in situ an anionic intermediate which is alkylated with an α -haloacetic acid moiety which is subsequently converted to the desired product, as well as valuable intermediates used in the process.

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INTERNATIONAL SEARCH REPORT

In national Application No

PCT/US 98/19359

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C255/46 C07C253/30 C07C227/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GARETH GRIFFITHS ET AL.: "Novel Syntheses of Gabapentin via Addition of Hydrocyanic Acid to Cyclohexylidenemalonate or Cyano(cyclohexylidene)acetate" HELVETICA CHIMICA ACTA, vol. 74, no. 2, 1991, pages 309-314, XP002100736 BASEL CH see page 312, scheme 5; page 313, line 51; page 314, lines 24 - 39 ---	1-60
A	US 5 132 451 A (REX A. JENNINGS ET AL.) 21 July 1992 cited in the application see the whole document --- -/--	1-60

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

21 April 1999

Date of mailing of the international search report

06/05/1999

Name and mailing address of the ISA

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Authorized officer

Zervas, B

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/19359

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>ATHUR G. SCHULTZ ET AL.: "Birch Reduction and Reductive Alkylation of Benzonitriles and Benzamides" JOURNAL OF ORGANIC CHEMISTRY, vol. 51, no. 25, 12 December 1986, pages 4983-4987, XP002100737 EASTON US cited in the application see page 4984, column 1, lines 5 - 21; page 4986, column 1, lines 6 - 62 -----</p>	1-60

INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No

PCT/US 98/19359

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU 633612 B	04-02-1993
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		NO 954930 A,B,	05-12-1995
		NO 954931 A,B,	05-12-1995
		NO 954932 A,B,	05-12-1995
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